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DERIVATIVES OF 1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLIC ACID

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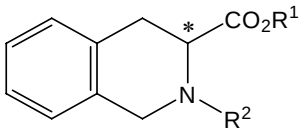
Abstract – The following derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid have been prepared in their (*S*)-form and as racemates: hydrochloride of methyl ester, *N*-carboxy anhydride, and *N*-acetyl derivative. All the substances were fully characterised by elemental analyses, ^{1}H and ^{13}C NMR spectra, and optical rotation, as the case may be; the *N*-carboxy anhydride was also characterised by means of X-Ray diffraction. Also identified was the intermediate of the reaction of the title acid with phosgene, the *N*-chlorocarbonyl derivative, and the respective methyl ester was prepared. The dioxopiperazine of the title acid was prepared and characterised both in pure (*S*,*S*)-form and in the form of a mixture of two racemates. The optically pure dioxopiperazine was prepared by a reaction of the *N*-carboxy anhydride in solid phase.

INTRODUCTION

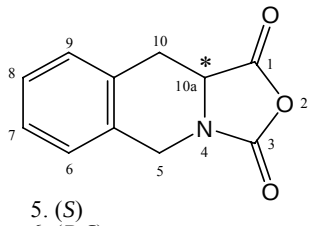
1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic acid) is a chiral α-amino acid, not occurring in nature, and easily accessible even in optically pure form. The interest in the derivatives of this acid is motivated by their very varied biological activities. Tic acid derivatives act as inhibitors in a number of enzymatic processes (for a survey, see Refs[1-8]); some of them (such as e.g. the HIV protease inhibitor Saquinavir®) have already been introduced into clinical practice.[9-11] The bridge formation of amino group with benzene ring restricts the conformational freedom of Tic acid, which allows preparations of peptides with defined tertiary structure.[2,12-15] Selected macrocyclic peptides containing Tic acid can even block the biosynthesis of peptides.[16,17] From the standpoint of biological activity also interesting are small

molecules containing the structural motif of Tic acid.[3,4,6,7,18-21] The present paper describes synthesis and identification of selected Tic acid derivatives, both in optically pure and in racemic forms.

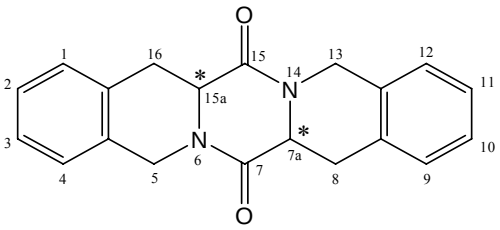
RESULTS AND DISCUSSION



1. (*S*), R^1=H, R^2=H
2. (*R*,*S*), R^1=H, R^2=H
3. (*S*), R^1=CH_3, R^2=H + HCl
4. (*R*,*S*), R^1=CH_3, R^2=H + HCl
7a,b. (*S*), R^1=H, R^2=COCl
8a,b. (*S*), R^1=CH_3, R^2=COCl
9a,b. (*S*), R^1=CH_3, R^2=$COCH_3$
10a,b. (*R*,*S*), R^1=CH_3, R^2=$COCH_3$



5. (*S*)
6. (*R*,*S*)



11. (7a*S*; 15a*S*)
12. (7a*R*,*S*; 15a*R*,*S*)
13. (7a*R*,*S*; 15a*S*,*R*)

The racemic Tic acid (**2**) was prepared by the Pictet–Spengler reaction from racemic phenylalanine and formaldehyde.[22] The esterification of Tic acid (**2**) with methanol proceeds almost quantitatively to give the ester (**4**). *N*-Carboxy anhydrides are usual intermediates in peptide syntheses. As a rule, they are prepared by reactions of α-amino acids with phosgene. This preparation procedure was also adopted for the pre- paration of *N*-carboxy anhydride (**5**) in several patents;[23,24] however, the prepared substance (**5**) was used further *in situ* without being identified and its physical constants determined. According to Ref.,[1] *N*-carboxy anhydride (**5**) was for the first time isolated in the yield of 66% after the reaction of Tic acid (**1**) with di(*tert*-butyl) dicarbonate and PCl_3. The procedure adopted by us for the preparation of compound (**5**) by the reaction of Tic acid (**1**) with a solution of phosgene in a mixture of THF and CH_2Cl_2 gives a 95% yield of *N*-carboxy anhydride (**5**) with higher mp and somewhat higher optical purity. The same procedure as that for the (*S*)-enantiomer was also adopted for the racemic *N*-carboxy anhydride (**6**), the yield being similar.

The structure of *N*-carboxy anhydride (**5**) was determined by means of X-Ray diffraction. An ORTEP view[25] is shown in Figure 1. The six-membered ring C3-C4-C5-C10-C11-N1 exhibits an envelope conformation ^{1}E with puckering parameters[26] of: Q_T = 0.418(2) Å, φ_2 = –10.9(5)°, θ_2 = 49.5(3)°. The other rings are essentially planar. The molecules, in the crystal, are linked in chains by means of short carbonyl-carbonyl dipolar interactions, C=O···C=O, of carboxy anhydride moieties as shown in Figure 2 having the O1···C2 distance of 2.954(3) Å much shorter than the sum of van der Waals radii of 3.22 Å.

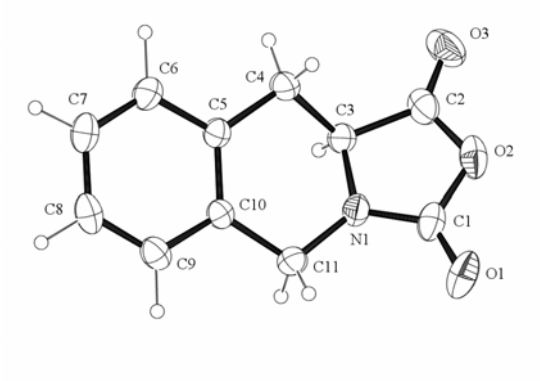


Figure 1. ORTEP view of (**5**) displaying thermal ellipsoids at 30% probability.

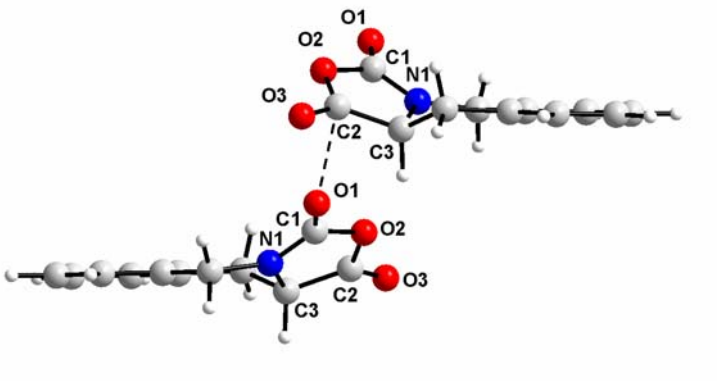


Figure 2. Dipole-dipole C1=O1···C2=O3 interactions in the crystal packing between carbonyl groups.

These attractive interactions, which can be competitive with hydrogen bonds, assume an important role in organic and biological systems for their molecular recognition properties.[27-31] In the crystal, the molecules form a layered structure (Figure 3).

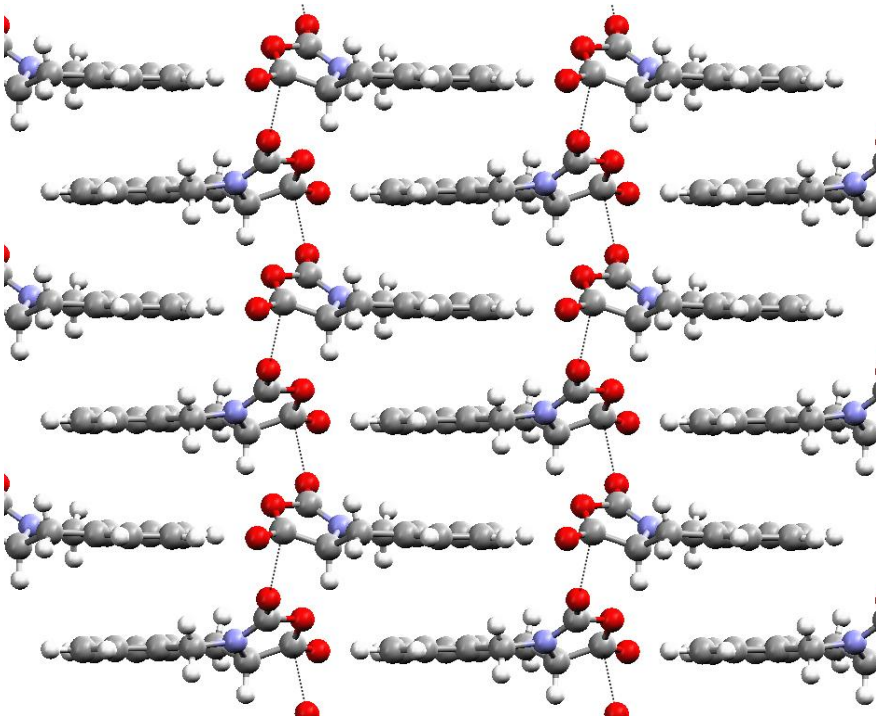


Figure 3. The crystal packing of **5** viewed down the crystallographic *a* axis.

The molecular structure determined by X-Ray is in accordance with the optimum conformation calculated at the level of B3LYP[32,33]/TZVP.[34]

We found out that the pure *N*-carboxy anhydride (**5**) is not obtained if, in the preparation of compound (**5**) and processing of the reaction mixture, the heating above rt is omitted. Besides the *N*-carboxy anhydride,

the reaction mixture contains further two structurally similar substances with a skeleton close to that of the starting Tic acid (according to ^{1}H and ^{13}C NMR spectra) but containing one additional carbonyl group (δ 150.26 and 149.09) of the carbamoyl chloride type (for *N*,*N*-dimethylcarbamoyl chloride[35] δ 148.2, for *N*,*N*-diethylcarbamoyl chloride[36] δ 148.5 in $CDCl_3$). The amount of these substances decreases with time, their ratio being maintained (**7a**/**7b** = 10/12); their transformation only produces *N*-carboxy anhydride (**5**). At enhanced temperature, the decrease in the amount of substances (**7a,b**) is fast, or, as the case may be, their formation cannot be observed at all. These substances (**7a,b**) were ascribed the structure of (3*S*)-*N*-chlorocarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. They are conformational iso- mers differing in the conformation of the –NCOCl group as the consequence of partial double bond character of NC bond. Carbonyl chloride (**7**) is an intermediate in the formation of *N*-carboxy anhydride, and it cannot be separated from the *N*-carboxy anhydride. Its structure was suggested by means of the NMR spectra.

In order to further confirm the structure of carbamoyl chloride, we also carried out the reaction of phosgene with the hydrochloride of ester (**3**). Also in this case, we observed formation of analogous isomeric carbamoyl chlorides (**8a,b**). These substances could be isolated and identified by their ^{1}H and ^{13}C NMR spectra and elemental analyses.

The hindered rotation causing formation of conformational isomers can also be observed in the spectra of methyl (3*S*)-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**9**) and racemic methyl ester (**10**) too.

Symmetrical dioxopiperazines can be prepared under mild conditions by a reaction of hydrochloride of ester of α-amino acid with *N*-carboxy anhydride in the presence of a base. Using this method, we prepared (7a*S*,15a*S*)-5,8,13,16-tetrahydro-7a*H*,15a*H*-6,14-diazapentacene-7,15-dione (**11**) in a yield of 52 % from compounds (**3**, **5**) and triethylamine. From the NMR spectra it is obvious that there takes place partial inversion of configuration as the consequence of the presence of acidic hydrogen atom next to the carbonyl group, diastereoisomer (**13**) being formed. The optical purity of compound (**11**) is 90 %. Dioxopiperazine (**11**) is also formed by 15 h boiling of *N*-carboxy anhydride (**5**) in toluene. However, the yield is only 56 %, the rest being formed by peptides. The optical purity of the dioxopiperazine (**11**) thus prepared is, according to the ^{1}H NMR spectra, better than in the previous case, namely 97 %. Surprisingly, the highest yield of dioxopiperazine (**11**) was obtained by 10 h heating of *N*-carboxy anhydride (**5**) at 100 °C in inert atmosphere without solvent. The crude product contains 98 % (7a*S*,15a*S*)-5,8,13,16-tetrahydro-7a*H*,15a*H*-6,14-diazapentacene-7,15-dione (**11**) with the diastereoisomeric purity of 100 %. The easy formation of dioxopiperazine (**11**) by heating *N*-carboxy anhydride (**5**) to temperatures below its mp without solvent can probably be explained by the character of the crystal lattice of *N*-carboxy anhydride, in which pairs of molecules are placed in layers with their anhydride groups oriented against each other (Figure 2).

The reaction of racemic *N*-carboxy anhydride (**6**) with racemic ester (**4**) produces two racemates of dioxopiperazine: (7a*S*,15a*S*) + (7a*R*,15a*R*) (**12**) and (7a*S*,15a*R*) + (7a*R*,15a*S*) (**13**). Using the method of addition of compound (**11**), we found out that the stereoisomers are present in this mixture at a ratio of **12**/**13** = 17/3.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

The NMR spectra were measured at 298 K with Bruker AVANCE 500 spectrometer equipped with 5 mm broadband probe at the frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) and with a Bruker AMX 360 spectrometer at the frequencies 360.14 MHz (^{1}H) and 90.57 MHz (^{13}C) in DMSO-d_6, $CDCl_3$, and D_2O. The ^{1}H NMR spectra were calibrated in $CDCl_3$ on hexamethyldisiloxane (δ 0.05), in DMSO-d_6 on the central signal of the solvent multiplet (δ 2.55), and on DSS in D_2O (δ 0.02). The ^{13}C NMR spectra were calibrated on the central signal of the solvent multiplet (δ 39.6 for DMSO-d_6, δ 77.0 for $CDCl_3$), and on DSS (δ 1.6) for D_2O. The carbon NMR spectra were measured in standard way and by means of the APT pulse sequence.

Melting points were determined with a Kofler hot stage microscope and were not corrected. The elemental analyses were carried out with a FISONS EA 1108 automatic analyser. Optical rotations were measured on PERKIN ELMER 341 Polarimeter at λ 589.3 nm and 298 K.

The crystal data for the compound (**5**) were collected at the room temperature using a Nonius Kappa CCD diffractometer with graphite monochromated Mo K_α radiation and corrected for Lorentz and polarization effects. The structures were solved by direct methods SIR97[37] and refined using full-matrix least-squares with anisotropic non-hydrogen atoms and isotropic hydrogens. All the calculations were performed using SHELXL-97[38] and PARST[39] inplemented in WINGX.[40]

Crystal data: (**5**), $C_{11}H_9NO_3$; monoclinic, space group $P2_1$, a = 6.8994(3), b = 7.1160(4), c = 10.0425(5) Å, β = 107.646(1)°, V = 469.85(4) Å^3, Z = 2, Dc = 1.436 g cm^{-3}. Intensity data collected with θ ≤ 30°; 2421 independent reflections measured; 1500 observed [I >2σ(I)]. Final R index = 0.0445 (observed reflections), Rw = 0.1110 (all reflections), S = 0.971.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 283185. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, Union Road, Cambridge CB2 1EZ, UK [fax: (+44)1223-336033, e-mail: deposit@ccdc.cam.ac.uk

The starting **(*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid** (**1**) (CMS Chemicals LTD), mp 331 °C (decomp), the content of 99.1% according to titration with $HClO_4$, and $[\alpha]_D^{20} = -175.8°$ (c = 1.1N aq NaOH), Ref.[22] gives $[\alpha]_D^{20} = -177.4°$ (c = 1.1N aq NaOH).

^{1}H NMR (D_2O) (as the *tert*-butylammonium salt prepared *in situ*) δ 7.23-7.09 (4H, m, arom.), 4.80 (bs, N^+H_3+NH+HDO), 3.98 (1H, d, H(1a), ^2J=16.3 Hz), 3.92 (1H, d, H(1b), ^2J=16.3 Hz), 3.40 (1H, dd, H(3), ^3J=4.5 Hz, ^3J=10.8 Hz), 3.02 (1H, dd, H(4a), ^2J=16.5 Hz, ^3J=4.5 Hz,), 2.81 (1H, dd, H(4b), ^2J=16.5 Hz, ^3J=10.8 Hz,), 1.13 (9H, s, $(C(CH_3)_3)$). ^{13}C NMR (D_2O) (as the *tert*-butylammonium salt) δ 177.37 (COO), 132.19, 131.94 (arom, 2xC_q), 126.73, 123.74, 123.66, 123.40 (arom, 4xCH), 55.19 (**C**HCO), 44.89 (N**C**$(CH_3)_3$), 44.02 (Ar**C**H_2N), 29.30 (Ar**C**H_2C), 27.90 (NC(**C**$H_3)_3$).

(±)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (**2**) was prepared according to Ref.,[22] yield 91%. ^{1}H and ^{13}C NMR spectra (*tert*-butylammonium salt) in D_2O were identical with the *tert*-butylammonium salt of compound (**1**).

Hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**) was prepared from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1**) and $SOCl_2$ in dry methanol by a known procedure[22,41] with practically quantitative yield. mp 248-250°C (decomp), (methanol-ether). Ref.[22] gives mp 250-255 °C, (decomp), (methanol-ether). The product recrystallised from a mixture of chloroform-ether melts at 261-263°C (decomp), $[\alpha]_D^{20} = -155.1°$ (c = 1, $CHCl_3$), $[\alpha]_D^{20} = -128.2°$ (c = 1, CH_3OH). Ref.[22] gives $[\alpha]_D^{20} = -104.1°$ (c = 1, CH_3OH). For the NMR spectral analysis, the product was washed with saturated solution of HCl in ether.

^{1}H NMR (DMSO-d_6) δ 10.03 (2H, br s, NH_2^+), 7.32-7.30 (4H, m, arom.), 4.41 (1H, d, H(1a), ^2J=16.2 Hz), 4.36 (1H, d, H(1b), ^2J=16.2 Hz), 4.61 (1H, dd, H(3), ^3J=5.2 Hz, ^3J=11.2 Hz), 3.35 (1H, dd, H(4a), ^2J=16.9 Hz, ^3J=5.2 Hz), 3.20 (1H, dd, H(4b), ^2J=16.9 Hz, ^3J=11.2 Hz), 3.86 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6) δ 169.08 (COO), 131.05, 130.70 (arom, 2xC_q), 129.12, 128.47, 127.98, 126.92 (arom, 4xCH), 53.53 (OCH_3), 53.41 (**C**HCO), 44.09 (Ar**C**H_2N), 28.27 (Ar**C**H_2C).

Hydrochloride of methyl (±)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**4**) was prepared from (±)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**2**) in the same way and in practically quantitative yield. Its mp is 250-252 °C (decomp), (methanol-ether), Ref.[41] gives mp 302-303 °C (decomp), (methanol- ether), and Ref.[42] gives mp 278 °C (chloroform-ether). For the NMR analysis, the product was washed with saturated solution of HCl in ether. ^{1}H and ^{13}C NMR spectra in DMSO-D_6 were identical with those of compound (**3**).

(10a*S*)-10,10a-Dihydro[1,3]oxazolo[3,4-*b*]isoquinoline-1,3(5*H*)-dione (**5**)**:** A suspension of 7.1 g (40 mmol) (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1**) in 100 mL of dry THF was treated with a solution of 8 g (80 mmol) of $COCl_2$ in 50 mL of CH_2Cl_2 added at –30 °C with vigorous stirring. The

reaction mixture was kept at the temperature of –30 °C for another 1 h and then stirred with spontaneous increase in temperature up to rt, and further stirred at rt overnight. The resulting clear solution was rid of all the solvents and rest of phosgene by means of vacuum distillation, keeping the temperature below 40 °C. The yield was 7.8 g (95 %) of yellowish crystals, mp 183-185 °C (cyclohexane), mp 152-153 °C (ether), $[\alpha]_D^{20} = -188.2°$ (c = 2.1, $CHCl_3$), Ref.[1] gives mp 150°C (ether) and $[\alpha]_D^{20} = -187°$ (c = 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.28-7.16 (4H, m, arom.), 4.93 (1H, d, H(1a), ^2J=16.6 Hz), 4.48 (1H, d, H(1b), ^2J=16.6 Hz), 4.36 (1H, dd, H(3), ^3J=4.7 Hz, ^3J=11.4 Hz), 3.31 (1H, dd, H(4a), ^2J=15.3 Hz, ^3J=4.7 Hz), 3.05 (1H, dd, H(4b), ^2J=15.3 Hz, ^3J=11.4 Hz). ^{13}C NMR ($CDCl_3$) δ 168.33 (C**C**OO), 150.73 (NCOO), 129.76, 129.74 (arom, 2xC_q), 129.57, 127.80, 127.62, 126.62 (arom, 4xCH), 54.54 (**C**HCO), 42.36 (Ar**C**H_2N), 30.45 (Ar**C**H_2C).

(10a±)-10,10a-Dihydro[1,3]oxazolo[3,4-*b*]isoquinoline-1,3(5*H*)-dione (**6**): Compound (**6**) was prepared in the same way as compound (**5**) with a yield of 90 %, mp 180-183°C (cyclohexane). ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were identical with those of compound (**5**).

Methyl (3*S*)-*N*-chlorocarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**8**): A suspension of 0.17 g (0.75 mmol) of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**) in 20 mL of dry THF was treated with a solution of 0.15 g (1.5 mmol) $COCl_2$ in 10 mL of CH_2Cl_2 added at the temperature of –30 °C with vigorous stirring. The reaction mixture was kept at the temperature of –30 °C for another 1 h and then stirred with spontaneous increase in temperature up to rt, and further stirred at rt overnight. The resulting clear solution was rid of all the solvents and rest of phosgene by means of vacuum distillation, keeping the temperature below rt. The yield was 0.19 g yellowish oily product (practically quantitative yield). The NMR spectral analysis showed that the product is a mixture of two isomers (the integral intensities are in the ratio **8a**/**8b** = 11/10). The unambiguous assignment of signals to the individual isomers was carried out by means of NOE. *Anal.* Calcd for $C_{12}H_{12}NO_3Cl$: C, 56.82; H, 4.77; N 5.52; Cl, 13.98. Found: C, 57.05; H, 4.95; N, 5.66; Cl, 13.69.

Isomer (**8a**): ^{1}H NMR ($CDCl_3$) δ 7.36-7.16 (4H, m, arom.), 4.96 (1H, d, H(1a), ^2J=16.0 Hz), 4.80 (1H, d, H(1b), ^2J=16.0 Hz), 5.24 (1H, dd, H(3), ^3J=3.4 Hz, ^3J=5.6 Hz), 3.31 (1H, dd, H(4a), ^2J=15.5 Hz, ^3J=3.4 Hz), 3.21 (1H, dd, H(4b), ^2J=15.5 Hz, ^3J=5.6 Hz), 3.64 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$) δ 169.74 (COO), 150.26 (NCOCl), 131.36, 131.03 (arom, 2xC_q), 128.26, 127.43, 127.29, 126.16 (arom, 4xCH), 55.50 (OCH_3), 52.71 (**C**HCO), 48.42 (Ar**C**H_2N), 31.07 (Ar**C**H_2C).

Isomer (**8b**): ^{1}H NMR ($CDCl_3$) δ 7.36-7.16 (4H, m, arom.), 4.86 (1H, d, H(1a), ^2J=16.4 Hz), 4.70 (1H, d, H(1b), ^2J=16.4 Hz), 5.21 (1H, dd, H(3), ^3J=3.6 Hz, ^3J=5.7 Hz), 3.33 (1H, dd, H(4a), ^2J=15.8 Hz, ^3J=3.6 Hz), 3.26 (1H, dd, H(4b), ^2J=15.8 Hz, ^3J=5.7 Hz), 3.65 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$) δ 170.06 (COO), 149.09 (NCOCl), 131.12, 130.91 (arom, 2xC_q), 128.06, 127.41, 127.26, 126.16 (arom, 4xCH), 57.68 (OCH_3), 52.84 (**C**HCO), 47.23 (Ar**C**H_2N), 31.52 (Ar**C**H_2C).

Methyl (3*S*)-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**9**): The synthesis was performed in analogy with Ref.[43] The reaction flask was charged with 5 g (22.0 mmol) of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**), 1.25 g (15.3 mmol) of anhydrous sodium acetate and 11.35 mL (120.4 mmol) of acetic anhydride. The suspension formed was stirred at a temperature of 50-60 °C for 1 h, whereupon the reaction mixture was poured in 50 mL of H_2O and immediately extracted with 3 × 25 mL of $CHCl_3$. The chloroform extract was partially concentrated and extracted once more with 50 mL H_2O. The organic phase was dried with anhydrous Na_2SO_4 and all the solvents were evaporated to leave an oily product. The product was further purified by flash chromatography (mobile phase: CH_3OH, stationary phase: silica gel 60 μm). After recrystallisation from cyclohexane with charcoal, the yield was 4.6 g (90%) white crystals, mp 93-96 °C, $[\alpha]_D^{20}$ = +35.6° (c = 1, $CHCl_3$). The NMR spectral analysis shows that the product is a mixture of two isomers (the integral intensities are in the ratio **9a**/**9b** = 5/2). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C 66.68; H, 6.61; N, 5.93.

Isomer (**9a**): ^{1}H NMR ($CDCl_3$) δ 7.22-7.11 (4H, m, arom.), 4.72 (1H, d, H(1a), ^2J=15.8 Hz), 4.66 (1H, d, H(1b), ^2J=15.8 Hz), 5.49 (1H, dd, H(3), ^3J=3.5 Hz, ^3J=6.3 Hz), 3.25 (1H, dd, H(4a), ^2J=15.9 Hz, ^3J=3.5 Hz), 3.11 (1H, dd, H(4b), ^2J=15.9 Hz, ^3J=6.3 Hz), 3.61 (3H, s, OCH_3), 2.25 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 171.39, 170.61 (2xCO), 132.10, 131.97 (arom, 2xC_q), 128.47, 127.15, 126.88, 126.00 (arom, 4xCH), 52.26 (**C**HCO), 51.06 (OCH_3), 46.31 (Ar**C**H_2N), 30.80 (Ar**C**H_2C), 21.91 (CH_3).

Isomer (**9b**): ^{1}H NMR ($CDCl_3$) δ 7.22-7.11 (4H, m, arom.), 4.93 (1H, d, H(1a), ^2J=17.3 Hz), 4.49 (1H, d, H(1b), ^2J=17.3 Hz), 4.78 (1H, dd, H(3), ^3J=2.8 Hz, ^3J=6.0 Hz), 3.34 (1H, dd, H(4a), ^2J=15.6 Hz, ^3J=2.8 Hz), 3.19 (1H, dd, H(4b), ^2J=15.6 Hz, ^3J=6.0 Hz), 3.60 (3H, s, OCH_3), 2.16 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.94, 170.54 (2xCO), 132.59, 131.00 (arom, 2xC_q), 128.00, 127.06, 126.74, 126.58 (arom, 4xCH), 55.67 (OCH_3), 52.61 (**C**HCO), 43.34 (Ar**C**H_2N), 31.82 (Ar**C**H_2C), 21.80 (CH_3).

Methyl (±)-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**10**): Compound (**10**) was prepared in the same way as methyl (3*S*)-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**9**) in the yield of 92 %. After flash chromatography, the product was isolated as an oily substance. The NMR spectral analysis shows that also in this case the product is a mixture of two isomers (the integral intensities are in the ratio of 5/2). The NMR spectra are identical with those of methyl (3*S*)-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**9**).

(7a*S*,15a*S*)-5,8,13,16-Tetrahydro-7a*H*,15a*H*-6,14-diazapentacene-7,15-dione (**11**)

Procedure A: The synthesis was performed in analogy with the procedures described in Refs.[1,44]: 0.16 g (0.78 mmol) of (10a*S*)-10,10a-dihydro[1,3]oxazolo[3,4-*b*]isoquinoline-1,3(5*H*)-dione (**5**) was added into a solution prepared by addition of 0.24 mL (1.74 mmol) dry NEt_3 to a solution of 0.20 g (0.89 mmol) of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**) in 10 mL dry CH_2Cl_2 at

–75 °C. The solution was stirred at –75 °C for another 2 h, whereupon the reaction mixture was stirred overnight with spontaneous increase in the temperature to rt. The obtained solution was concentrated, and the evaporation residue was dissolved in 50 mL of toluene. The toluene solution was extracted with 20 mL H_2O and then with 20 mL 3% hydrochloric acid. Then it was dried with anhydrous Na_2SO_4 and rid of all the solvent. After recrystallisation from methanol, the yield was 0.13 g (52 %) of yellowish crystals. The NMR spectra indicate that the product has been isolated in 90% diastereoisomeric purity.

Procedure B: 0.16 g (0.78 mmol) of (10a*S*)-10,10a-dihydro[1,3]oxazolo[3,4-*b*]isoquinoline-1,3(5*H*)-dione (**5**) was dissolved in toluene and boiled 12 h. After evaporation of all the solvent, the yield was 0.15 g of brownish product. The NMR spectra indicate that the product is present in the isolated mixture in an amount of 56% (The rest are peptides.). The diastereoisomeric purity of product is 97 %.

Procedure C: 0.16 g (0.78 mmol) of (10a*S*)-10,10a-dihydro[1,3]oxazolo[3,4-*b*]isoquinoline-1,3(5*H*)-dione (**5**) was heated without solvent under argon at 100 °C for a period of 10 h. The product was then analysed by NMR spectrum without purification. It was found out that the isolated mixture contains 98 % of the product with diastereoisomeric purity of 100 %. By dissolving in $CHCl_3$ and removal of insoluble portions by filtration, and after evaporation of all the $CHCl_3$, the yield was 0.15 g (95 %) pure diastereoisomer of product, mp 198-200°C, $[\alpha]_D^{20} = -378.1°$ (c = 1, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N 8.80. Found: C, 75.49; H, 5.91; N, 8.58.

^{1}H NMR ($CDCl_3$) δ 7.29-7.17 (8H, m, arom.), 5.41 (2H, d, H(5a), H(13a), ^2J=17.1 Hz), 4.36 (2H, d, H(5b), H(13b), ^2J=17.1 Hz), 4.31 (2H, dd, H(7a), H(15a), ^3J=3.6 Hz, ^3J=12.2 Hz), 3.47 (2H, dd, H(8a), H(16a), ^2J=16.2 Hz, ^3J=3.6 Hz), 3.03 (2H, dd, H(8b), H(16b), ^2J=16.2 Hz, ^3J=12.2 Hz). ^{13}C NMR ($CDCl_3$) δ 164.11 (2xC**C**ON), 132.31, 131.38 (arom, 2x2xC_q), 128.80, 127.13, 127.10, 126.35 (arom, 2x4xCH), 55.75 (2x**C**HCO), 44.05 (2xAr**C**H_2N), 34.23 (2xAr**C**H_2C).

5,8,13,16-Tetrahydro-7a*H*,15a*H*-6,14-diazapentacene-7,15-dione (a mixture of diastereoisomeric racemates (**12**) and (**13**)): A mixture of isomers of 5,7,12,14-tetrahydro-6a*H*,13a*H*-5a,12a-diazapentacene- 6,13-dione was prepared by Procedure **A** from compounds (**4**) and (**6**) as the (7a*S*,15a*S*)-5,8,13,16- tetrahydro-7a*H*,15a*H*-6,14-diazapentacene-7,15-dione (**11**) in the yield of 63 %, with mp 183-191 °C. The NMR spectral analysis shoved that the product is a mixture of two diastereoisomers (in the isolated mixture, the integral intensities of the diastereoisomers are in the ratio of **12**/**13** = 17/3). The structure of major isomer was confirmed by addition of (7a*S*,15a*S*)-5,8,13,16-tetrahydro-7a*H*,15a*H*-6,14-diazapentacene-7,15-dione (**11**) directly into the mixture of the diastereoisomers. *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.72; H, 5.66; N, 8.67.

Diastereoisomer (**13**): ^{1}H NMR ($CDCl_3$) δ 7.30-7.15 (8H, m, arom.), 5.43 (2H, d, H(5a), H(13a), ^2J=17.3 Hz), 4.38 (2H, d, H(5b), H(13b), ^2J=17.3 Hz), 4.31 (2H, dd, H(7a), H(15a), ^3J=3.2 Hz, ^3J=12.2 Hz), 3.54

(2H, dd, H(8a), H(16a), ^{2}J=16.2 Hz, ^{3}J=3.2 Hz), 3.06 (2H, dd, H(8b), H(16b), ^{2}J=16.2 Hz, ^{3}J=12.2 Hz). ^{13}C NMR ($CDCl_3$) δ 164.11 (2xC**C**ON), 132.31, 131.38 (arom, 2x2xC_q), 128.84, 127.13, 127.03, 126.30 (arom, 2x4xCH), 55.41 (2x**C**HCO), 44.41 (2xAr**C**H_2N), 34.22 (2xAr**C**H_2C).

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